## Phylogeny

Human NTRK3 (TrkC) is classified within the Tyrosine Kinase (TK) group, Receptor Tyrosine Kinase (RTK) family, NTRK subfamily (bertrand2017crystalstructuresof pages 1-5).  
The kinase domain shares 71.9–78.3 % sequence identity with its paralogues TrkA and TrkB, with TrkB being the closest homologue (bertrand2017crystalstructuresof pages 1-5).  
Trk receptors show higher overall homology to the insulin-receptor branch than to other RTK clades (bertrand2017crystalstructuresof pages 1-5).  
Orthologous genes have been documented in mouse, where targeted deletion leads to proprioceptive and cardiac defects (barbacid1994thetrkfamily pages 1-2).  
An evolutionary conserved Trk-like receptor is present in the snail Lymnaea stagnalis, illustrating conservation from invertebrates to vertebrates (wiesmann2001nervegrowthfactor pages 4-6).

## Reaction Catalyzed

Protein-L-tyrosine + ATP ⇌ Protein-L-tyrosine-phosphate + ADP (wai1999molecularcharacterizationof pages 28-33).

## Cofactor Requirements

Catalytic activity depends on ATP binding and divalent metal ions such as Mg²⁺ or Mn²⁺, as typical for receptor tyrosine kinases (bertrand2017crystalstructuresof pages 1-5).

## Substrate Specificity

A universal consensus motif has not been defined for NTRK3; specificity is primarily inferred from its autophosphorylation pattern (wai1999molecularcharacterizationof pages 28-33).  
Documented autophosphorylation sites include Tyr516 in the juxtamembrane region and Tyr705, Tyr709, Tyr710 within the activation loop, together with Tyr820 in the C-lobe (wai1999molecularcharacterizationof pages 28-33).  
Phosphorylation of the activation-loop tyrosines is essential for full catalytic competence of the receptor (cunningham1997autophosphorylationofactivation pages 11-12).

## Structure

TrkC is organised into an N-terminal extracellular region containing a cysteine-rich segment, leucine-rich repeat domain 2, and two immunoglobulin-like domains 4 and 5 that mediate high-affinity NT-3 binding (wiesmann2001nervegrowthfactor pages 4-6).  
This is followed by a single transmembrane helix, a juxtamembrane KFG motif, and an intracellular kinase domain harbouring a variable kinase-insert domain (barbacid1994thetrkfamily pages 1-2, bertrand2017crystalstructuresof pages 5-9).  
X-ray structures of the kinase domain have been solved in complex with inhibitors, e.g. PDB 3V5Q and PDB 6KZC, both adopting an inactive DFG-out conformation (bertrand2012thecrystalstructures pages 2-5, somwar2020ntrkkinasedomain pages 11-11).  
No apo (ligand-free) crystal structure of the TrkC kinase domain is currently available (bertrand2017crystalstructuresof pages 5-9).  
The gatekeeper residue is a bulky phenylalanine that stacks against the DFG phenylalanine, occluding the hydrophobic back pocket (bertrand2012thecrystalstructures pages 2-5).  
The αC-helix is rotated outward in the inactive state, disrupting the conserved Lys-Glu salt bridge, whereas the hydrophobic regulatory spine is aligned only in modelled active conformations (bertrand2017crystalstructuresof pages 15-18).  
The kinase-insert domain is unresolved in existing structures and differs in sequence and length among Trk paralogues, representing a potential isoform-selective element (bertrand2017crystalstructuresof pages 15-18).

## Regulation

Ligand binding of neurotrophin-3 to the extracellular domains induces receptor homodimerisation and trans-autophosphorylation of intracellular tyrosines (bertrand2017crystalstructuresof pages 1-5, wai1999molecularcharacterizationof pages 28-33).  
Autophosphorylation at Tyr516 creates a docking site for SHC and the p85 subunit of PI3K, while phosphorylation at Tyr705, Tyr709 and Tyr710 within the activation loop is required for catalytic activation, and Tyr820 recruits PLCγ (wai1999molecularcharacterizationof pages 28-33).  
Negative feedback is mediated by Cbl family E3 ubiquitin ligases, which bind phosphorylated TrkC and promote its ubiquitination and lysosomal degradation (tang2022negativeregulationof pages 1-2).  
An alternatively spliced isoform containing a 14-residue insert lacks catalytic activity and functions as an endogenous dominant-negative regulator (wai1999molecularcharacterizationof pages 28-33).  
Conformational switching between DFG-in (active) and DFG-out (inactive) states, influenced by nucleotide or inhibitor binding, further modulates kinase activity (bertrand2017crystalstructuresof pages 9-15).

## Function

TrkC is prominently expressed in central and peripheral nervous system tissues and plays critical roles in neuronal survival, differentiation and synaptic plasticity (barbacid1994thetrkfamily pages 1-2, bertrand2017crystalstructuresof pages 1-5).  
It also contributes to cardiac development, as evidenced by phenotypes in knockout mice (barbacid1994thetrkfamily pages 1-2).  
Upon NT-3 binding, the receptor activates the RAS/ERK, PI3K/AKT and PLCγ pathways via recruitment of adaptor proteins such as SHC, GRB2/SOS, PI3K-p85 and PLCγ (wai1999molecularcharacterizationof pages 28-33, jiang2021developmentofsmallmolecule pages 6-9).  
Time-resolved phosphoproteomic analyses in neuroblastoma cells confirm robust activation of these downstream signalling cascades following TrkC stimulation (maher2024atemporal(phospho)proteomic pages 1-2).

## Inhibitors

Clinically approved ATP-competitive pan-Trk inhibitors larotrectinib and entrectinib inhibit TrkC with nanomolar potency and are used to treat NTRK fusion-positive cancers (jiang2021developmentofsmallmolecule pages 1-6).  
Additional chemotypes such as EX429 and GNF-20 bind to either DFG-in or DFG-out conformations but exhibit limited isoform selectivity (bertrand2017crystalstructuresof pages 9-15).  
The 6KZC structure has been utilised to model the impact of kinase-domain mutations on the sensitivity to type I versus type II inhibitors (somwar2020ntrkkinasedomain pages 11-11).  
Next-generation inhibitors are in development to overcome acquired resistance mutations (jiang2021developmentofsmallmolecule pages 30-49).

## Other Comments

Chromosomal fusions such as ETV6-NTRK3 drive secretory breast carcinoma, infantile fibrosarcoma and congenital mesoblastic nephroma through constitutive kinase activation (jiang2021developmentofsmallmolecule pages 1-6).  
Somatic point mutations within the activation loop have been reported in colorectal, lung, breast and pancreatic cancers and may confer ligand-independent signalling (wood2006somaticmutationsof pages 4-7).  
Co-overexpression of TrkC and NT-3 transforms fibroblasts, underscoring the necessity for tight regulatory control (wai1999molecularcharacterizationof pages 28-33).  
Lack of isoform selectivity in current pan-Trk inhibitors raises concerns about central nervous system adverse effects (bertrand2017crystalstructuresof pages 9-15).

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